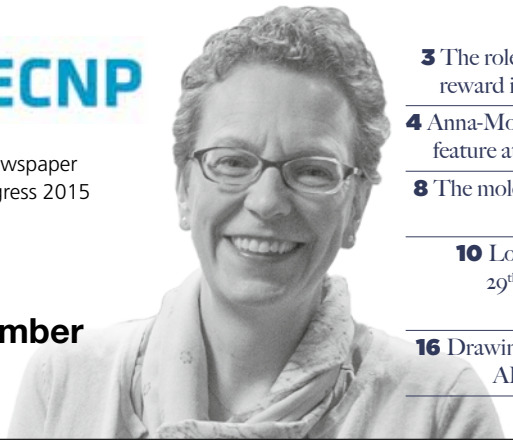
ECNP

The official newspaper of ECNP Congress 2015

Issue 4
Tuesday
1 September 2015



ECNP DAILY NEWS

PLENARY LECTURES

PL.05: **Brain Prize award lecture** Auditorium **Tuesday** 11:15–12:00

ECNP hosts Brain Prize lecture on impulsivity & compulsivity

The Grete Lundbeck European Brain Research Prize is awarded to one or more active scientists who have contributed exemplary work to the field of European neuroscience. Alongside Giacomo Rizzolatti and Stanislas Dehaene, in 2014 the Prize was jointly awarded to Trevor W. Robbins (University of Cambridge, UK) for pioneering research on the higher brain mechanisms underpinning complex human functions.

The ECNP Congress is honoured to feature a plenary lecture by Professor Robbins, held today, in which he will detail his comprehensive work in the field, as well as going into more specific detail about his study of impulsivity and compulsivity.

"I am very pleased to have been offered this plenary lecture," Professor Robbins told *ECNP Daily News*. "I think I am the first person to win the Brain Prize who is actually a neuropsychopharmacologist, so one might say I am the first to 'represent' the ECNP!"

Describing his work, Professor Robbins began by framing his overarching interest in the higher brain mechanisms that affect human function and behaviour: "What we are really interested in is core neurobehavioural deficits, if you like, i.e. changes which produce some of these bizarre psychiatric symptoms we know about," he said.

> "Work we have done [has] identified a kind of top-down inhibitory circuitry which seems to malfunction in stimulant drug addiction."
>
> Trevor W. Robbins

"In a way this is relevant to the NIH initiative RDoC [Research Domain Criteria], because that has essentially thrown out the old diagnostic and statistical manual approach to psychiatry – that of categorical diagnosis – and instead what they want to put in is a more neuroscientifically-informed means of quantifying and characterising problems that psychiatric patients have."

Professor Robbins suggested that the underpinnings behind this new strategy were likely three-fold, with

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Continued from page 1

the first reason being that psychiatric genetic understanding is making 'painfully slow' progress. Delving deeper, he noted that one of the problems behind this is that phenotypic definitions are very weak, being largely based on ill-defined categories, questionnaire measurements and self-report scales.

"The second point that I think is crucial to neuropsychopharmacology is that phase III trials are a disaster," he said. "Why? Well first of all I would say because they are using outdated means of measurement. They are very insensitive scales, and trying to obtain significant changes on these scales to prove efficacy of candidate compounds is difficult.

"What is also very important is the sheer heterogeneity of phase III trials. Not only because the measures are so weak, but also because in any case you need to demonstrate efficacy across a range of cultures or places, meaning trials are enormous, and recruitment is very heterogeneous. You may have subgroups of patients who are quite well-treated by compound 'X', but then they are counterpointed by another subgroup who doesn't respond at all, and maybe even gets worse."

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> Trevor W. Robbins

The third reason Professor Robbins underlined was that surely by now we must be learning that treatment should be done before damage occurs. Using Alzheimer's, psychosis or even drug addiction as examples, he stressed that it is imperative to catch diseases early, before damage becomes irreversible. "So the future will be detecting these problems early on, and intervening – perhaps psychologically as much as pharmacologically," he said. "And of course that means taking a whole new perspective on how you detect the vulnerabilities which lead to problems.

Impulsivity and compulsivity

While Professor Robbins has been interested in the wider reaches of all of these important considerations, his core work focuses on impulsive/compulsive disorders specifically, including addiction, OCD and ADHD.[1,2]

While some people may categorise impulsivity and compulsivity together, Professor Robbins cautioned that this is probably a mistake. "There are overlaps," he said, "in that they both involve some kind of top-down control – probably inhibitory – which prevents you from blurting out unwanted things, or perseverating in something which is not good for you, but overall I think different circuits are involved."

As he detailed, impulsivity can be briefly described as the tendency to act prematurely, without foresight, although can be further subdivided into 'waiting' and 'stopping' impulsivity, depending on distinct fronto-striatal substrates. It is associated with most forms of drug and alcohol abuse, and is thought to be linked to addictive behaviour.[1] Compulsivity, on the other hand, is a hypothetical trait where actions are repeated, persistently, despite them not providing benefit to the individual, or even indeed causing adverse consequences.[2]

In his lecture, Professor Robbins will focus in part on impulsive and compulsive circuits in the rat brain, and how they are modulated neurochemically. "An interesting note is that certain forms of impulsivity seem to be treated with atomoxetine, which is a noradrenaline reuptake inhibitor, whereas forms of compulsivity are often treated with high doses of selective serotonin reuptake inhibitors, as in OCD, where people are treated with higher-than-antidepressant-doses of SSRIs," he said.

"So these are the paradigms that I want to share with the audience: the definition of neurobehavioural constructs with relevance to particular syndromes; showing where they are different and where they overlap; and through the circuitry, trying to get new target identification for big pharma or small pharma to use their molecules."

In terms of how impulsivity and compulsivity present, while it is ultimately down to how one defines each trait, there is likely a little impulsivity and compulsivity in all of us, and indeed impulsivity may even be a pre-existing personality trait.[1] Commenting on this notion, Professor Robbins suggested that presentation may first largely depend on the genetic cards any one person is dealt, and then will be further compounded by environmental factors that can lead to expression of impulsive or compulsive tendencies.

"An interesting example is if you look inside a family, and you see there is a tendency for drug abuse there," he said. "What is it that protected the family member who did not become addicted? There must be something else in their makeup which prevented them from becoming addicted. Maybe that is an environmental factor – for example one of the drug-abusive family members was exposed to a certain type of stressor – or maybe it is just that while both parties are exposed to the possibility, only one of them has the additional ability to resist the tendency.

> "[Impulsivity and compulsivity] both involve some kind of top-down control – probably inhibitory – which prevents you from blurting out unwanted things, or perseverating in something which is not good for you, but overall I think different circuits are involved."
>
> Trevor W. Robbins

"I have some fairly graphical evidence of that, from work we have done which has identified a kind of top-down inhibitory circuitry which seems to malfunction in stimulant drug addiction. Specifically, what seems to happen is that, in first-degree relatives, who have the same kind of brain problems and behavioural tendencies, they tend to activate this area much more – even more than healthy controls. So it is as though they are compensating for this problem they have. The interesting issue is how long can you go on doing that? You have to exert this additional effort to resist the phenotype as it were. So I think these are all interesting questions."

For more information on the Brain Prize, head to www.thebrainprize.org

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PLENARY LECTURE

PL.03: **Plenary lecture – the role of motivation and reward in mental disorders** Auditorium **Monday** 11:15–12:00

Motivation and reward in mental disorders

The role of motivation and reward in mental disorders was explored in depth during yesterday morning's plenary lecture by Andreas Heinz (Charité Universitätsmedizin Berlin Campus Charité Mitte, Berlin, Germany). Discussing the role of aberrant reward prediction across nosological boundaries, he explained the relevance of this novel understanding to decision-making in individuals and clinical treatment.

Professor Heinz began by saying that the expansion of diagnostic categories within manuals such as the ICD and DSM has paralleled a growing understanding that disorder boundaries do not signify their possessing distinct biological fingerprints: "An alternative ways to look at these disorders is – as always in science – by a reduction approach, trying to capture some basic mechanisms. This is now, with the RDoC [Research Domain Criteria] approach, of public interest, but it is also much older. People like [Peter J] Lang suggested that we could map human emotions, and also the learning mechanisms associated with them, rather simply."

Understanding learning mechanisms underlying positive and negative affect, he explained, is valuable in that it creates a link between biology and behaviour in health and disorder. New computational models facilitate this and relieve the reliance upon feedback from study participants which, he noted, is heavily variable depending on the person's ability to express the way that they feel.

Exploring the role of dopamine, he explained that the monoaminergic systems arise from the brainstem, from where neurotransmission elsewhere is modulated. Citing the work of Schultz et al. (1993), he explained that dopamine release can reflect an error of reward prediction (the degree to which a reward is surprising).[1] More recently computational methods have proven useful in confirming that dopamine levels increase when a surprise reward is experienced. Furthermore, when a reward is predicted, the conditioned cue is as positive in inducing motivation as the award originally was – such as was demonstrated by Ivan Pavlov.

> "An alternative ways to look at these disorders is – as always in science – by a reduction approach."
>
> Andreas Heinz

The nature of reward introduces an affective component to the drivers of learning, which Professor Heinz summarised by saying: "There is a French philosopher, [Jacques] Lacan, who said, 'Desire disappears in the moment of fulfilment, and the fulfilment is quite boring.' He must have been a good observer of his own dopamine system!"

He went on to show that healthy individuals demonstrated ventral striatal activation during reward anticipation after being conditioned to a particular cue. Ventral striatal activation also occurred, albeit to a lesser degree, in loss prediction.

This paradigm has now been applied to many mental disorders, he continued: "If there is a true dimensional perspective to reward, you should find alterations in reward anticipation, not only in those groups with dopamine dysfunction, but in a series of patient groups."

Indeed, Professor Heinz and colleagues went on to show reduced activation of the ventral striatum in alcoholism, schizophrenia and major depression.[2] "Across all of these groups, the less you are able to encode expecting a reward, the more you are depressed or show some signs of negative mood. That could be one axis into this mood, and indeed dysfunction of reward anticipation could contribute to it.

"Below these superficial similarities there are of course fundamental differences. In schizophrenia, for example, we assume that there is a network dysfunction – maybe temporal-limbic alterations in processing of novel versus old cues, and then indirectly this stimulates dopamine release."

Thus, while hypoactivation in response to reward cues could describe symptoms of apathy, Professor Heinz submitted that phasically-driven, stress-associated peaks of dopamine lead to errors in reward prediction which might explain patients' aberrant attribution of salience to cues that leads to delusional thinking.

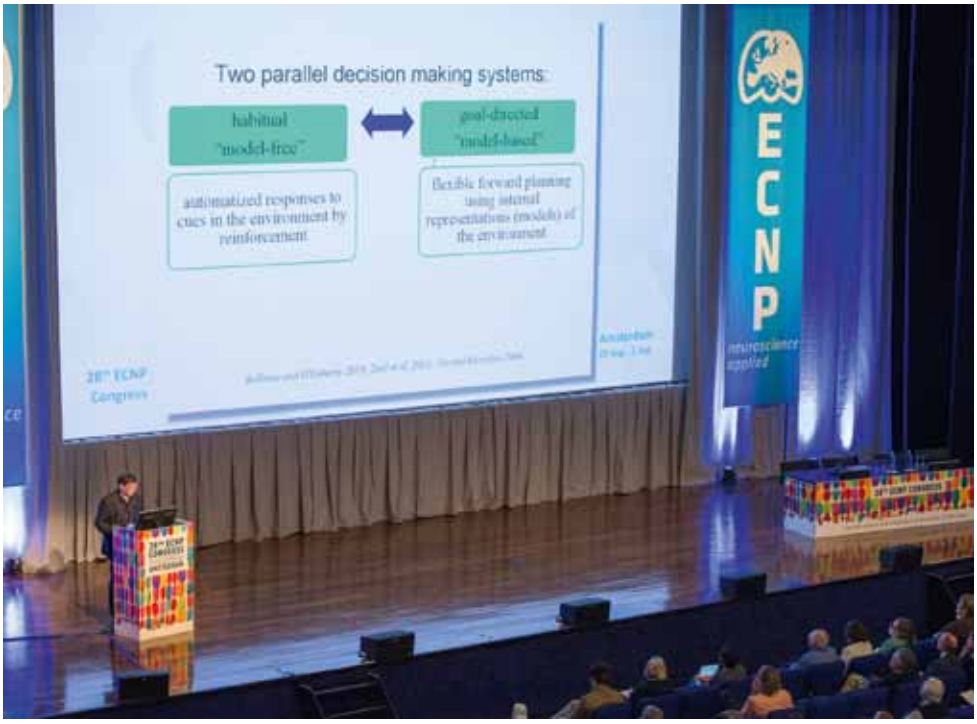
The reverse is expected in alcoholism, wherein, explained Professor Heinz, reduced levels of the dopamine D2 receptor have been observed in early alcohol abstinence: "Dopamine release goes down the moment that alcohol intake is stopped," he said. "They tend to remain downregulated, recovering in days to weeks. We previously observed that the longer they take to recover, the higher the relapse risk."

Further investigation into reward prediction errors in alcoholism revealed the important role of communication between the dorsolateral prefrontal cortex (DLPFC) and the ventral striatum in the process of learning: "Prediction error encoding, ventral striatal activation, in alcohol-dependent patients, seemed to be okay. But it was rather the bottom-up information processing to some area of the DLPFC that we found altered.

"In healthy controls, when you do well there is a lot of interaction between these areas. When you don't do well, there is little interaction. The larger the difference between these two states, the faster that people learn. This is because you can make more sense of your feedback; you can transfer the information in states in which you are successful to areas that monitor your behaviour. In alcohol-dependent patients, this difference was blunted."

Decision-making, he continued, can be investigated in a more complex fashion to try to understand the underlying processes of relapse, and the roles of goal-directed versus habitual decision-making. "When patients with alcohol dependence are detoxicated, they should not do what they always did when they got in a bad mood (like drink), they have to cognitively monitor themselves and tell themselves that they want to maintain abstinence. This is quite relevant clinically, because we assume that in addiction it is usually more shifted to the habitual behavioural patterns.

"Humans in general mix those models – habitual and goal-directed – and with alcohol dependent patients it was particularly difficult for them to uphold a reaction that is usually good but in rare cases is bad. Maybe that is something that we could use for therapy – to strengthen their ability to monitor what they are doing and to make choices that sometimes have negative outcomes."



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Anna-Monika lectures present the forefront of depression research

The Anna-Monika Prize is awarded bi-annually to clinical scientists who have made outstanding contributions to the understanding of the neurobiological underpinnings of depression. The key goal of the award is to encourage the development of novel treatment options for affective disorders. This afternoon, Anna-Monika prize-winners Ned Kalin (University of Wisconsin, USA) and Carmine Pariante (Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK), will be receiving their prizes live on stage, before presenting their recent work to the audience.

PLENARY LECTURE

PL.06: **Anna-Monika Award lecture I – Anxious temperament** Auditorium **Tuesday** 14:00–14:45

Translational approaches to understanding anxious temperament

Anxious temperament is common in the normal population and is characterised by a dispositional tendency to respond to potentially threatening situations with heightened anxiety and physiological reactivity. Understanding the determinants of such traits has proven fruitful in teasing apart the contributing factors to the early life development of depressive and anxiety disorders. In the final plenary lecture of the congress, taking place this afternoon, Professor Kalin will discuss early-in-life anxious temperament from the perspective of its mediating developmental mechanisms, as well as an opportunity to develop novel treatments aimed at early interventions to prevent the development of anxiety and depressive disorders.[1]

"Evidence points to this early extreme anxious disposition as being a very prominent risk factor for the later development of anxiety, depression, and comorbid substance abuse," said Professor Kalin during an interview with *ECNP Daily News*. "Human studies have shown, including some work from our group, that young children and toddlers that exhibit this disposition have a 50% likelihood of developing a psychiatric problem. So this is a very strong marker of early life risk for these disorders."

Alarming though this may be, these findings nevertheless suggest a way of rerouting learned behaviours and responses in such children away from their anxieties and inhibitions. In order to do this, it is necessary first to understand what exactly the genetic and environmental factors are that tend to result in the development of extreme anxious temperament. Combining early identification with novel interventional strategies are part and parcel of the strategy to develop new diagnostic and treatment methods aimed at preventing the later development of anxiety and depression in adolescence and adulthood.

Professor Kalin's group has extensively studied non-human primates in order to come up with their hypotheses. "Non-human primates provide an excellent model of this extreme disposition in children," he explained. "We have also been performing parallel studies in children.

"Non-human primate studies allowed us to first develop a reliable model of this anxious temperament disposition, at the behavioural and emotional level. We characterised these behaviours to make sure that the model maps on exactly to the human condition. Then, using imaging techniques that are commonly used in humans, we were able to identify the underlying brain circuit that is over-active in individuals that have this early life disposition."

This brain circuit ties together distributed regions of the brain including the central nucleus of the amygdala, the anterior hippocampus, and the orbitofrontal cortex. By altering the function of the different components of the circuit using lesion strategies as well as molecularly targeted viral vectors, the group is beginning to investigate the causal components of the overactivity. "We were able to inactivate cells in the central nucleus region of the amygdala," said Professor Kalin. "This demonstrated a reduction in the extreme anxious temperament – a normalisation suggesting that overactivity in this region is not only associated with the extreme anxious temperament, but that it is causally related to it.

> "Evidence points to this early extreme anxious disposition as being a very prominent risk factor for the later development of anxiety, depression, and comorbid substance abuse."
> Ned Kalin

> "Using imaging techniques that are commonly used in humans, we were able to identify the underlying brain circuit that is over-active in individuals that have this early life disposition."
> Ned Kalin

"Once we understand some of the critical components of the circuit, we can then ask what the molecular underpinnings are that drive overactivity of the circuit. We can also ask questions about how much of the tendency to be dispositionally anxious, both at the behavioural level and at the brain level, is inherited versus how much is acquired through learning and experience.

"We have been able to do that. We have been able to establish the components of the circuit that underlie this extreme condition that are heritable in the same way that the anxious temperament is heritable. Finally, we have been able to use molecular strategies to identify altered genes that are over- or under-active in the brain regions that are critical for mediating this anxious temperament."

These causal links are crucial in developing novel treatments that target genetic vulnerabilities; conversely, they can help us understand which behavioural or environmental interventions might work best for altering patterns of behaviour that are more likely to lead to anxiety and depression in later life.

And this work holds implications for adults, too. For those with refractory psychiatric problems, gene altering strategies – already being adopted in some neurotherapeutic arenas – is a bold but perhaps effective direction where few alternatives exist.

Throughout all of this, the heterogeneity of brain and behaviour is an important consideration, as is the heterogeneous and complex interrelation between stress and other risk factors of anxiety and depression: "There are studies that have shown that some individuals have high levels of stress hormones that are not necessarily extreme in their behaviours," noted Professor Kalin. "But there are others that have extreme behaviours, but only moderate levels of stress hormones. So it is this heterogeneity that is going to be important."

When it comes to intervention in childhood, Professor Kalin foresees behavioural rather than medical intervention as critical for ameliorating anxious temperament: "For

children who have psychiatric problems that are really disabling, if other strategies don't work, then this is when we start to think about medicines. We don't really know as much about the effect of medicines on children's future development at the moment, so if we can reduce exposure to medicine that is a good thing.

"For those children that have not demonstrated any behavioural problems, but who show signs of a risk factor, we could start to think about behavioural interventions. These include helping parents improve the way that they are interacting with their children, helping expose children to situations that will help them to overcome anxiety. It also seems that early exercise may be very helpful – these are the kinds of things we are thinking about."

Professor Kalin will present his plenary lecture, 'Anxious temperament: results from a translational neuroscience approach,' this afternoon between 14:00 and 14:45 in the Auditorium. At the beginning of the session, Professor Kalin and Professor Pariante will receive their Anna-Monika Prizes live on stage.

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PRECLINICAL RESEARCH

S.28: **Understanding the role of inflammation in the pathophysiology of depression** Emerald **Tuesday** 15:00–16:40

What role does inflammation play in depression?

Carmine Pariante has worked extensively in understanding the relationship between stress and inflammation in depression. During his Anna-Monika lecture, he will discuss the hypothesis that, in some patients, stress may be related to long-lasting changes in immune functioning which perpetuate the reduced neurogenesis characteristic of major depression.[1]

"We have known for many years that patients with major depressive disorder (MDD) have abnormalities in the secretion of hormones, which we term neuroendocrine abnormalities," he told *ECNP Daily News*. "The most reproduced abnormality is that of the increased activity of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in hypersecretion of cortisol."

While this has been accepted knowledge for around thirty years, more recent interest in the role of the immune system in MDD has led Professor Pariante and others to develop an understanding of the relationship between neuroendocrine and immune abnormalities: "There is evidence that patients with depression – especially patients who have severe MDD and who are resistant to conventional antidepressant treatment – have a high level of inflammatory biomarkers.[1]

"The question that my research group and others have been trying to address is whether there is a relationship between the high level of cortisol and the high level of inflammation, which we often find in the same patient."

Curiously, cortisol bears anti-inflammatory properties – its synthetic analogues, such as dexamethasone, are commonly used as anti-inflammatory agents. Puzzled by this contradiction, the group went on to discover that while cortisol levels in the blood may be high, the receptor mediating its anti-inflammatory action may not necessarily be active. This may result in further activation of the immune system.

Understanding how inflammation affects brain function, and neuronal function in particular, is the object of Professor Pariante's latest work in cellular and animal models: "We have been showing that high levels of inflammation can reduce neurogenesis and can also reduce synaptogenesis and dendritogenesis," he said. "So in general it has the effect of inhibiting neuroplasticity. We think that this effect may be one of the mechanisms by which high levels of inflammation produces depressive symptoms."

The fact that antidepressants are only effective in a subset of patients with MDD suggests that a plurality of mechanisms are at play, and indeed evidence provided by Professor Pariante's group and others seems to suggest that high levels of inflammation correlate negatively with antidepressant efficacy. Stressing the preliminary nature of these findings, he noted some of the possible therapies that may emerge with further research: "For those that are treatment resistant, we could have a strategy that the patient is investigated for their immune function early in their course of treatment. If they have normal levels of inflammatory markers, they may be more likely to respond to standard anti-depressants.

"But if they have high levels of inflammation, they may be less likely to respond, so they may be a candidate for adjuvant or more complex strategies for treatment-resistant depression, including anti-inflammatories. We still don't yet have enough data to justify such a clinical approach, and we cannot underestimate the potential complications of co-prescribing antidepressants and anti-inflammatories."

Unfortunately, evidence supporting the use of drugs that directly target the cortisol receptor has not been consistent; however, as Professor Pariante explained, with such a complex set of factors at play, it could simply be the case that studies to date have not looked at a specific enough sample of MDD patients. "It is possible that targeting the glucocorticoid receptor directly may only work in a small subgroup of patients that are particularly severe," he said. "However, we do know that using anti-inflammatory drugs to directly dampen the inflammation may have an anti-depressant action. There has been some clinical trial showing some promising results, but we need to replicate those data in larger samples."

The causal relationship between inflammation and depression remains unclear, while the association between early life stresses and psychopathologies including MDD are well accepted. Professor Pariante has published on early stressors in childhood as well as in utero, looking at the potential effects that depression in expecting mothers can bestow on the foetus.[2]

"Pregnancy is obviously in itself a physiological state, characterised by changes in hormones and in the immune system," he noted. "We and others have found evidence of, again, higher levels of cortisol and higher levels of inflammatory biomarkers in women who are depressed in pregnancy.

"The interesting thing about depression in pregnancy is that not only does it affect the woman, but also potentially it has a biological effect on the foetus in utero because of the changes in the uterine environment. So one of the questions that I have tried to address in my research is whether the increased level of cortisol and increased inflammation in depressed women in pregnancy may have an effect on the development of the stress response of the offspring, and perhaps increase the risk of the offspring themselves developing depression later in life."

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>
> Carmine Pariante

TRANSLATIONAL RESEARCH

S.27: **Towards neuroimaging markers for diagnosis, prognosis and treatment prediction** Forum **Tuesday** 15:00–16:40

fMRI is key in boosting treatment prediction

The ins and outs of neuroimaging as a tool for diagnosis, prognosis and prediction of effective treatment will be explored this afternoon, with speakers lining up to share their experiences in using novel techniques and technologies to forward the field.

In his presentation, session co-chair Guido van Wingen (Academic Medical Center, Amsterdam, the Netherlands) will be focussing primarily on how we can use new imaging techniques to address the psychiatry's widespread inability to effectively predict which patients will benefit from which drugs. "We are in a paradigm where we have evidence-based medicine – that is that we treat patients with medications or other treatments that work in 50% of the cases or so," he said.

With that in mind, patients are treated with full knowledge that around half of them will not respond to treatment on the first attempt, with only minor increases in overall success as new drugs, doses or other treatments are pursued. "If we did know in advance that patient 'A' would get better with medication 'Y', then we would obviously give the patient that medication," commented Dr van Wingen.

"This is a general problem for almost all treatments in psychiatry. There is a long history in which we have tried to predict treatment outcomes, but so far that has been largely based on correlations across patients. The problem is that the predictive power for an individual patient is very low, yet you want to treat this particular patient that is sitting in your office; you want to know for this particular patient whether their medication will work or not. So we have a new paradigm in which we can actually personalise treatment towards specific patients."

In his previous work, Dr van Wingen explored the use of electroconvulsive therapy (ECT) for patients with depression that was resistant to many different types of treatment, including psychotherapy, multiple medications etc. While invasive, ECT is a relatively effective treatment that can be initiated at the end of a treatment line. "And still approximately 50% of the patients will recover, even though they did not respond to any other type of treatment," he said.

Dr van Wingen noted that it is quite remarkable that 50% of patients still recover even though all other treatments have failed. He added: "And maybe 20% or so will respond a little, but still 30-40% will not respond at all. Thus you might want to actually avoid it, i.e. putting patients through an invasive procedure that is associated with temporary cognitive side-effects, and is also quite costly, given it is likely to not work in many patients."

Following on from this work, Dr van Wingen has been harnessing the promising power of functional MRI (fMRI) – a technique that has been available for two decades, and is now being tested for its use in more 'personalised' medicine. "Resting-state fMRI allows users to make a series of scans that can track blood flow, and thus unveiling some of the communicative pathways between distant brain areas. Crucially, this communication is disturbed in patients with a variety of disorders, thus it can be used to distinguish, on an individual patient level, those with depression from healthy individuals."

Coupled to the power of machine learning – a branch of artificial intelligence in which computational learning and pattern recognition comes into play – computer programmes are able to tease apart the subtle differences in communicative blood maps that are otherwise impossible to see with the naked eye. Impressively, in testing this has taken the predictive power of an effective treatment from 50%, to 85%: "The American Psychiatric Association considers all biomarkers with what we call sensitivity and specificity of above 80% to be clinically useful," noted Dr van Wingen.

> "There is a long history [in psychiatry] in which we have tried to predict treatment outcomes, but so far that has been largely based on correlations across patients."
>
> Guido van Wingen

Commenting on the availability of the resting-state fMRI scanning functionality, Dr van Wingen continued: "Every centre with an MRI scanner can actually do this; it is not much different than taking a typical MRI scan. You have an anatomical scan, to see brain structures, and in addition you can make an fMRI scan. This is what any centre could do, although they maybe would need to buy an additional software package from their machine vendor.

With respect to what the next steps may be for expanding more on fMRI's power in treatment-response prediction, Dr van Wingen commented: "At this point we are in the discovery phase, i.e. we are in the process of developing these kinds of biomarkers. But once we have those for particular cases, and we see generalisations across hospitals, then not only could you perform this type of imaging via an extra software package, but you could also imagine that one day maybe data will be uploaded via the internet to a server, and in turn giving you the output for a particular patient, within a certain percentage of accuracy."

> "fMRI will be a generic approach to all types of clinical problems in psychiatry, and all types of disorders."
>
> Guido van Wingen

Turning to today's session as a whole, Dr van Wingen briefly introduced some of the other focal points: "There will be one speaker mainly talking about psychosis, and the prediction of long-term outcome. Some psychotic patients will do very well in the near future, whereas others will say in a chronic state, and will need chronic care – which is costly. So if you know that upfront, then you can recruit additional care for those who need it ahead of time.

"Maaike Rive will talk about dissociating between different types of disorders. Typically we do that in psychiatry with the DSM criteria, on a clinical basis, but in some cases it is really difficult. And what she will show is how to classify unipolar and bipolar disorder using functional neuroimaging. For instance, if a person enters the hospital in a manic state then is quite clear, but if they enter in a depressed state, and they didn't go through a

manic state already, you don't know whether you are dealing with a depressed patient or a potential bipolar patient. And that is where it might be quite useful to harness brain imaging patterns, because the treatment pathway for depression is different than for bipolar disorder."

Dr van Wingen offered his closing thoughts on the future for fMRI, commenting: "People are always thinking that MRI is expensive, but when factoring in the time that clinicians will lose in failed treatments, it is far cheaper. And of course it is best for the patient to be helped as soon as possible.

"I do think fMRI will be a generic approach to all types of clinical problems in psychiatry, and all types of disorders. It could be used to classify patients to a particular disorder, for instance dissociating major depression from bipolar depression, or to predict the long-term outcome, for example in psychosis, perhaps looking at whether the psychosis will be a one-time phenomenon, or might lead to a more chronic state, or schizophrenia, and so on. It could also be used to predict all types of treatment outcome: be they medication, psychotherapy or, as I am presenting, electroconvulsive therapy."

TRANSLATIONAL RESEARCH

S.23: Stress as a risk factor: how much is enough? **Forum** Tuesday **09:00–10:40**

Stress is 'two-faced' factor in mental health

Stressful life events impact on brain and body function, and represent major risk factors for stress-related psychiatric disorders, delegates will hear this morning in a symposium that puts this 'hidden danger' centre stage.

In her work, Zhen Yan (State University of New York at Buffalo, NY, USA) has been looking at the 'two faces of stress', namely chronic versus acute, with specific consideration of the epigenetic mechanisms and rescue strategies for detrimental stress effects.

"In the beginning we were thinking about studying the effect of acute stress, because there are already a lot of studies that have been done on chronic stress," she told *ECNP Daily News*. "So we thought we could see what stress was doing in the brain – especially in the cortical area, and to our surprise, acute stressed animals had a strongly enhanced glutamate transmission."

She continued: "When we dug further into the mechanisms, we found that it has something to do with the trafficking of Glu receptors, and then we also found there were signalling molecules involved in the process."

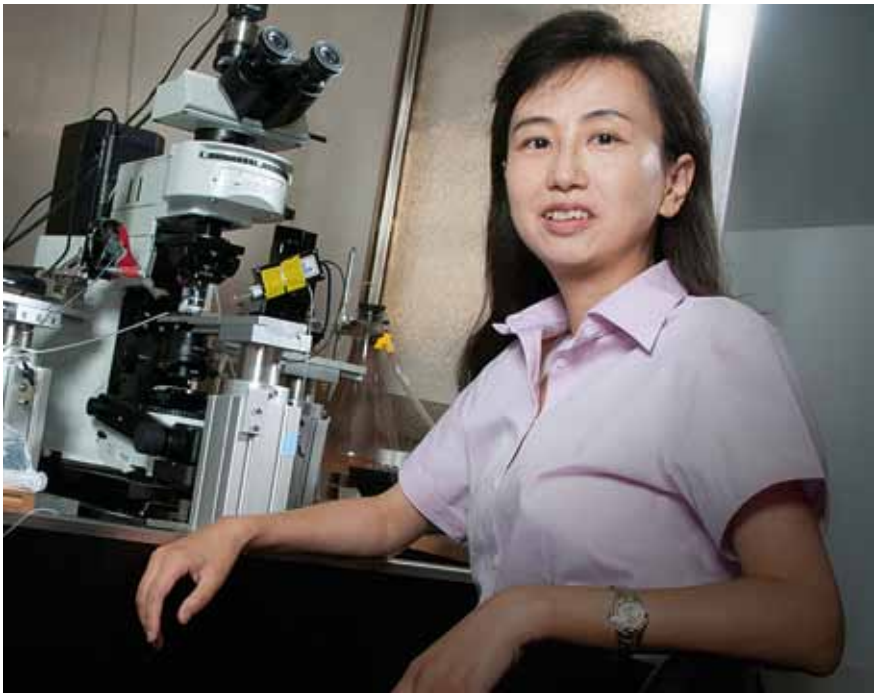
After further behavioural studies investigating the importance of this enhanced glutamate transmission in the prefrontal cortex, Dr Yan's group observed that the animals had enhanced performance in working memory. "This is mediated by the prefrontal cortex," she explained, "so that is a very good correlation.

"Then we used some tools to manipulate the key molecules involved in glutamate transmission, and we found that when we blocked the enhanced glutamate response, we would also block enhanced cognitive function. So it has a very causal relationship: we know that if you can enhance the response mediated by pyramidal neurons – the principle neurons in this area – then you will have better cognitive function."

Dr Yan noted that when this work was first submitted for publication, a lot of criticism surrounded it, with many arguing that stress is "always a bad thing", thus how could Dr Yan's group even suggest that it may potentiate some cognitive aspects? "And then they said that chronic stress is more related to mental disorders, so we should look into that," recalled Dr Yan.

"We thought it was very difficult to find a mechanism of chronic stress, so we gave animals repeated stress, for just one week (sub-chronic) using adolescent animals which seemed to have higher sensitivity to stress. Results showed a very dramatic loss of synaptic function, especially glutamate transmission, in these animals even after just one week of repeated stress."

Dr Yan detailed how these animals showed impaired recognition memory, brought on by repeated stress-induced synaptic depression, via increasing ubiquitin/proteasome-mediated degradation of NMDA and AMPA receptor subunits.



"We looked deeper at the potential mechanisms," said Dr Yan, adding that, in this case, active glucocorticoid receptor (GR) had increased binding to the glucocorticoid response element (GRE) of the Histone Deacetylase 2 (HDAC2) promoter, resulting in the upregulation of HDAC2.

As such, Dr Yan underlined that the inhibition or knockdown of HDAC2 blocks the chronic stress-induced impairment of synaptic transmission, AMPAR expression and recognition memory. Furthermore, inhibition of HDAC2 blocks the transcriptional activation of the E3 ubiquitin ligase Nedd4 and GluR1 ubiquitination in repeatedly stressed animals, via a mechanism involving histone methylation at the level of the Nedd4 promoter.

> "These results have provided an epigenetic mechanism and a potential rescue strategy for the detrimental effects of repeated stress."
>
> Zhen Yan

"There is a strong surge of the ubiquitination after chronic stress, and then after that the key subunit of Glu receptors are ubiquitinated and degraded," she said. "So if we can block those ubiquitinations, using for example I interferon to knock down those E3 ligases, then we block the degradation of Glu receptors, and block the damaging effects on cognitive function."

She concluded: "These results have provided an epigenetic mechanism and a potential rescue strategy for the detrimental effects of repeated stress."

CLINICAL TREATMENT

S.25: **Pharmacological enhancement of fear extinction in anxiety disorders** Auditorium **Tuesday** 15:00–16:40

Molecular mechanisms of memory

Normally memories of emotionally-arousing and stressful events are well retained; this is important from an evolutionary point of view, for behavioural adaptation. However, in some individuals, such as those with post-traumatic stress disorder (PTSD), memories are vividly and inappropriately expressed. Unravelling the molecular and cellular mechanisms that underlie enhanced memory formation of stressful events is therefore highly relevant.

This afternoon Harm Krugers (UvA SILS Center for Neurosciences, Amsterdam, the Netherlands) will be presenting a captivating insight into the molecular and mechanisms of memory and learning. In advance of his talk, when *ECNP Daily News* caught up with him to speak about his research, he began by saying: "Our research focus is largely on hormones and neuromodulators, like corticosteroid hormones and norepinephrine that are released after stress exposure. Corticosteroid hormones are released after stress through activation of the hypothalamus-pituitary-adrenal (HPA)-axis and alter brain function via activation of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs)."

Adding, "We know that corticosteroids can promote learning and memory of emotionally arousing events, and the main question is how do these hormones enhance memory and learning?"

The action of corticosteroid hormones on AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-type glutamate receptors is important for storage of information.[1] Corticosteroid hormones modulate synaptic content though dynamically regulation of AMPA receptors: they can be inserted into synapses and then transported back to the cytosol."[2]

Describing the goals behind his research, Dr Krugers said: "We wanted to understand the routes AMPA receptors use to reach the synapse, and which routes are relevant for synaptic transmission and fear memory." Using electrophysiology, molecular biological, pharmacological and behavioural tools he studied molecular mechanisms of corticosteroid hormone regulation of AMPA receptor at synapses and their involvement in memory consolidation. His results showed that exposure to stressful events and elevated corticosteroid hormone levels target key mechanisms that are involved in synaptic plasticity, i.e. via AMPA receptors, and fear-memory formation.

> "It is important to get a better understanding of how emotionally arousing events are remembered – in some people too well, and why in others there is not enough extinction between these memories."
>
> Harm Krugers

Dr Krugers went on to stress the importance of a better understanding of how emotionally-arousing events are remembered. Specifically, why they are remembered so well in some individuals, and in others there is not enough extinction between these memories. This leads to the question of where does this variability come from?

The HPA-axis is programmed in early life and its activation determines synaptic function and enhances contextual fear later in life. Adverse events occurring in early life are considered important risk factors for the subsequent development of anxiety disorders and psychopathology. Dr Krugers and his research group were interested in understanding how early life adversity regulates contextual fear and the sensitivity of synapses, using low levels of maternal care as a model of early life adversity. They compared rodent offspring of mothers that exhibited low levels of maternal care to offspring of those that exhibited high levels of maternal care: they found that the less-cared-for offspring had enhanced memories for fearful events, and that synapses were differentially sensitised to stress hormones.

> "Our results show that the early postnatal period is one that determines the long-lasting sensitivity of synapses to stress hormones, and that this is modulated by the amount of maternal care."
>
> Harm Krugers

"We focused on negative events in the early postnatal period in mice and rat pups (equating to early childhood), studying the level of maternal care. Our results show that the early postnatal period is one that determines the long-lasting sensitivity of synapses to stress hormones, and that this is modulated by the amount of maternal care."[3]

It is of great interest to ascertain whether this process can be modulated, reflecting the ability to overcome detrimental affects of early life adversity on learning and memory. Using antagonists of corticosteroid receptors, Dr Krugers and co-workers investigated whether these stress-induced changes to learning and memory could be reversed, which he described: "In terms of behaviour and the expression of fear, we already

know that the actions of stress hormones on fear memory foundation are also mediated by corticosteroid receptors and by blocking their action we can prevent some of the effects of corticosterone.[4] It is possible that MRs and GRs have differential effects on memory consolidation, but the evidence shows that fear memory can definitely be interfered with."

To avoid the obfuscating effects of sex hormones on stress responses, early life adversity and synaptic events, Dr Krugers' studies are mainly performed in male animals, but effects of gender are still absolutely relevant. Literature on depression from human studies suggests there is an additional risk of developing stress-related psychopathologies such as depression in females, and to some extent the sex hormones regulate the synapses and cognition differently males and females.

> "... stressful events and elevated corticosteroid hormone levels target key mechanisms that are involved in synaptic plasticity, i.e. via AMPA receptors, and regulate memory formation."
>
> Harm Krugers

The discovery of potential opportunities for intervening with the memory process has great translational potential, as there is evidence showing that the expression of fear can be modulated when fear memories are retrieved. Dr Krugers explained: "During retrieval, fear memories are transiently labile, and there is a time window that offers a possibility to interfere with memory either pharmacologically or behaviourally."

Dr Krugers finished by describing memory retrieval in the context of cognitive behavioural therapy in patients suffering from anxiety disorders and other related disorders. Reconsolidation offers a time window of opportunity in which memories can be updated and stored again to potentially weaken or even erase the expression of fear. Research indicates that exploiting the plasticity of fear memory is necessary to advance the treatment for anxiety disorders and PTSD[5], with a pharmacologically-induced and/or or exposure-based psychotherapy. "If a person undergoes a stressful event and a psychopathological problem develops, a couple of weeks or years later, by retrieving the fearful event you might target disorders such as PTSD."

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NOMENCLATURE SESSION

NS.01: **How the Neuroscience Based Nomenclature can change my practice** Emerald **Tuesday** 12:15–13:00

A pocketful of wisdom: the continuing growth of the NbN

Those behind the scenes of ECNP's Neuroscience-based Nomenclature (NbN) project have worked tirelessly for the best part of a decade to bring the new nomenclature into force at last year's congress, with the release of the handbook and app. But their work is not yet done: further extensions are planned to the app, in terms of both content and availability.

Intrinsic to its continuing relevance, the NbN will continue to evolve to reflect the latest neuroscientific and clinical understanding. The old nomenclature, initiated in the 1960s, turned out to be confusing and confused and has since then hampered clinical choice-making and patient adherence.

Those involved are very proud to present the fruits of over seven years of labour, said taskforce leader Joseph Zohar (Chaim Sheba Medical Center, Israel), speaking to *ECNP Daily News*: "We are giving the clinician all the information in their pocket. The NbN will be updated at least once a year, to reflect the cutting edge knowledge about neuroscience."

The NbN now includes four additional dimensions, explained Professor Zohar, including approved indication according to major regulatory bodies such as the FDA and EMA. "We also added the efficacy and side effects," he continued. "This second dimension highlights situations where compounds are short of approval for formal indications, although there is evidence to support its use (e.g., in expert guidelines).

"We have a third additional dimension which is the practical note. This summarises the clinical knowledge that has been prioritised by filtering through the Task Force. The last additional dimension is the neurobiology which is derived from empirical data and divided into preclinical and clinical."

Other features are yet to be developed fully, such as the much-anticipated paediatric-specific version of the NbN, work towards which will commence in 2016. A neurology dimension is also anticipated at a later stage.

> "The NbN will be updated at least once a year, to reflect the cutting edge knowledge about neuroscience."
>
> Joseph Zohar

Updates to the search engine since the original launch of the app has improved usability, a crucial element in thoroughly informing clinicians' decision-making, whilst enabling them to easily learn about pharmacological aspects of drugs. "The clinician can not only search for a specific indication by name (and this could be generic or brand), they can also search any combination of the dimensions," explained Professor Zohar.

The translation of the app is another key step in its dissemination. With the Spanish and Japanese translations on the brink of completion, Professor Zohar expected that these versions will be up and running in the coming months, with plans to continue translating into different languages in the years to come.

Emphasising the importance of feedback, Professor Zohar went on: "We would like to get access to the wisdom of the clinicians, because their feedback is so important – we encourage and welcome everybody to use the specific feedback component of the app that is built in."

The NbN marks a collaboration, unprecedented in its uniqueness as much as its scale, between the five major international organisations with specific interests in neuropsychopharmacology – the colleges of Europe (ECNP), America (ACNP), and Asia (AsCNP), along with the International college (CINP) and the International Union of Basic and Clinical Pharmacology (IUPHAR).

With the world of psychopharmacology on its side, it is hoped that 2016 will see the twenty major journals that publish in the field of neuropsychopharmacology recommending the adoption of the NbN for those submitting papers. "We hope that the field will also use this nomenclature," said Professor Zohar. "We hope for it to be the language that we use now – moving from indication-based language with its marketing influences to pharmacology and neuroscience-driven nomenclature."

The new NbN website can be visited at http://nbnomenclature.org. You can also download the app from https://www.ecnp.eu/projects-initiatives/nomenclature.aspx

ECNP

SPC Chair for the 29th ECNP Congress

Looking ahead to Vienna 2016
Interview with Astrid Linthorst

Next year will see Vienna playing host to the 29th ECNP Congress, and preparations are already very much underway, both logistically and scientifically. *ECNP Daily News* spoke to Astrid Linthorst (University of Bristol, UK), the incoming Chair of the 2016 Scientific Programme Committee (SPC), to discuss the development of the programme and the new features appearing at the ECNP Congress next year.

The 2016 programme has been determined and the process of inviting speakers is about to start. A wealth of submitted symposium proposals has allowed the SPC to establish a stimulating and wide-ranging programme. The programme is a clear reflection of the mood of the scientific community, explained Professor Linthorst: "When you look at all the symposia, you get a very good idea of where the field is heading.

"In the programme for Vienna many exciting topics will be covered and I am happy to already reveal a few: Social stress and psychopathology; Improvement of antidepressant treatment outcome; Inflammation in psychosis; Role of CYP enzymes in psychiatric disorders; Emotion recognition in neurodegenerative disorders; New targets for treating alcohol dependence; and Predictive biomarkers for psychiatric disease in young people. Many symposia will look not only from the clinical but also from the preclinical perspective. Furthermore, we have many, many other inspiring and really interesting symposia as well, including seven Educational Update sessions."

> "In the programme for Vienna many exciting topics will be covered and I am happy to already reveal a few."
>
> Astrid Linthorst

Programme development begins approximately two years before the congress – a clear insight into the gargantuan nature of the process. The SPC Chair sets up a committee of around 16 individuals from major disciplines within the fields of neuropsychopharmacology and neuroscience. These committee members play a decisive role in shaping the programme.

"It is very important to have people on the committee who are active researchers, active clinicians, and who know where the field is going with input from all kinds of other people as well," noted Professor Linthorst. "We also look that the committee members are from different countries, because ECNP really wants to reflect that it is a European organisation. That is also good because they will be able to tell us who the people are in their own countries that are doing new and exciting research."

The 2016 SPC met in April and June of this year in preparation for Vienna. Before the first meeting, all proposals were ranked and scored by SPC members, so that they could be discussed during the meeting. "This is a whole-day process," said Professor Linthorst. "We look at scores, average scores and outliers, and discuss them. This is the first round of selection, and we meet two months later to make sure we are happy with the decisions we made in the first place and to fine-tune the programme.

> "It is very important to have people on the committee who are active researchers, active clinicians, and who know where the field is going."
>
> Astrid Linthorst

"We ask, is the programme balanced? Is it scientifically balanced, and balanced with respect to speakers from different countries? ECNP is also very committed to promoting women in science, so one of our goals is to have a programme with a good number of female scientists presenting."

Having had to reject a large number of excellent proposals in previous years due to the very simple issue of time and space constraints, next year's ECNP Congress will include an extra seven symposia. In this way, six parallel symposia will take place during each half-day where previously only five took place.

A second addition to the programme is the new feature aimed at clinicians, 'Top Papers,' in which an expert in the field will succinctly address and discuss the top four or five papers that have emerged during the year within their scientific discipline. Six different topics will be covered in Vienna, allowing psychiatrists and other clinical workers to gain an insight into the research going on in their field of expertise.

Wim van den Brink, who chairs the SPC for the third and final time this year, remains on next year's SPC as past-chair. With her thoughts on continuing his good work, Professor Linthorst said: "He has done a terrific job, because during the past three years he has ensured that the programme is at the forefront of science. He has also made sure that the programme is of great interest to psychiatrists – the people really working in the clinic – but also to clinical and basic researchers alike. There is a good balance for meeting the different interests of all those attending the congress, and this is something I hope to continue."

"Wim is enthusiastic, as well as being very good at finding top speakers for the keynote and plenary sessions. I can only say that it is a big challenge for me to succeed such an excellent chair, but my SPC members for Vienna are definitely an enormous support!"

See you in Vienna!

29TH ECNP CONGRESS | 17-20 SEPTEMBER 2016 VIENNA

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COMMENTARY

Neuroscience-based Nomenclature (NbN)

Where is the NbN headed in the future?

Having played a large role in the expansion of the NbN (see page 9) to include neurological disorders, Gitte Moos Knudsen (Copenhagen University Hospital Rigshospitalet, Denmark) spoke to *ECNP Daily News* to share her thoughts on the rationale for the project and its expansion, and how it will continue its growth in the future.

Fundamentally, the project accompanies the evolving dialogue between patient and practitioner within an increasingly global society that shares information freely via the internet. The role that the NbN will play in all of this, explained Professor Knudsen, is something that will continue to emerge as it is put into broader practice: "With such a new approach, we must be prepared that it will invariably take some time, but the more mature and disseminated the project becomes, the more it will take on its own life.

"We are at a stage where we are prepared to disseminate it, not only language-wise, but also to disseminate it into other brain disorders. This makes complete sense, because many of the drugs used in psychiatric disorders are also being used in neurological disorders."

This, she explained, really comes down to the neuroscience-based effects on the brain of such drugs. And much can be learned from such a crossover of perspectives, from brain disorders, to psychiatric disorders and to neurological disorders.

"This neuroscience-based approach is useful," she continued. "A clear example of this within neurology is Parkinson's disease that is caused by a deficient dopamine production by cells in the midbrain. The symptoms can be effectively ameliorated by intervention with precursors of dopamine, so that we can substitute what is lacking in the brain.

"In doing so, we have patients that experience side-effects, particularly in the late stages. They can develop psychosis with hallucinations, based in the medication they receive for their dopamine deficiency, but we now have compounds available that can be used to treat those psychotic episodes. One is pimavanserin, a serotonin-2A inverse agonist, i.e., a compound acting in the opposite way to the hallucinogenic compounds that act by stimulating the serotonin-2A receptor. Pimavanserin has now been proven to be helpful for those particular patients. This is a completely neuroscience-based approach."

Education is the NbN's raison d'être for doctor and patient alike, with patient involvement being critical to bringing about improvements in their adherence and self-reflection. "It will not only take a lot of effort to educate doctors in how to use the NbN, but it will also take a lot of effort so that we have more educated patients in the long run. It has been shown that the better educated patients are about their own disease, the better for them.

"It is about understanding questions such as, why do I get this drug, what is it good for, what kind of effects might I anticipate, and what will happen if it doesn't work. All of these considerations are really important to the patient."

Of course, this will not always be possible, especially for patients experiencing psychosis or dementia, for example. In these cases, it may be family members or guardians that will benefit from such education. In any case, the NbN provides a welcome and rigorous alternative to the sprawling flurry of information that can crop up via internet search engines.

"That body of experience out there, which all clinicians use all the time...could bring out new aspects that are not already in the NbN handbook."

Gitte Moos Knudsen

Looking forward, Professor Knudsen praised the inclusion user feedback for the evolution of the NbN's content: "The app is meant to be interactive so that clinicians, no matter who or where they are, can give their feedback to the information that is provided. That body of experience out there, which all clinicians use all the time (but which is not necessarily documented), is going to be very interesting to watch as it could bring out new aspects that are not already in the NbN handbook.

"Each clinician has her or his own experience, and this is not something that you can look up in a text book. What you find in a drug catalogue may not capture the real picture. The app opens up this new dimension of feedback."

Awards abound at ECNP Dinner!

The ECNP Dinner, held at the Cobra Museum in Amstelveen on Sunday night, featured an award ceremony in which the ECNP Certificate, and the six ECNP Fellowship Awards, were presented to their new owners. Congratulations to all of this year's winners!

(From left) The 2015 ECNP Fellowship Award winners: Christina Dalla, Andreas Menke, Eldar Hochman, Annamaria Cattaneo, Błażej Misiak and Dina Popovic

ECNP Certificate winner Christian Imboden

CLINICAL TREATMENT

S.05: **Electroconvulsive therapy – achieving and maintaining the benefit** Auditorium **Sunday 09:00–10:40**

ECT reconsidered

Modern techniques for severe depression

As the World Health Organisation (WHO) details, depression is a leading cause of disability worldwide, affecting approximately 350 million people. Evidence now indicates that approximately 60–70% of depressive patients respond to, or remit during, first-line pharmacological interventions, meaning that a substantial remainder become treatment resistant, leading to an increasing interest in non-pharmacological strategies.

Furthermore, this severely ill and vulnerable group are often suicidal,[1] so treatment is of utmost urgency, and in these cases, brain stimulation techniques like electroconvulsive therapy (ECT) can be very effective.

ECT involves passing an electric current are through the brain, intentionally triggering a brief seizure and chemical alterations that rapidly abate symptoms of depression. ECT dates back to the beginning of modern biological psychiatry, when it was developed by Ugo Cerletti, an Italian neurologist.[2] Much of the historical stigma attached to ECT is based on early treatments, whereby high doses of electricity were administered to patients without anaesthesia, leading to memory loss, fractured bones and other serious side effects. But contemporary use of anaesthesia, as well as advances in implementation, makes modern ECT a safe and highly effective procedure, and huge strides have been made to minimise the transient cognitive and memory side effects.

Our current understanding of ECT is that the antidepressant effect is partially mediated by seizure-induced neurotrophic effects, resulting in increased rates of neurogenesis, synaptogenesis, and glial proliferation, particularly in the hippocampus. Nevertheless, ECT still suffers something of an image problem in certain reaches of the media.[3]

"Our research demonstrated that high-dose unilateral ECT had fewer effects on autobiographical memory."

Declan McLoughlin

With all of this in mind, Sunday played host to a panel of eminent speakers examining modern ECT methods for treatment and maintenance of severe depression. *ECNP Daily News* was fortunate to be able to reach out to all four of the speakers before this captivating session to discuss their findings on advances in ECT treatment.

Speaking first in the session was Declan McLoughlin (Trinity College Dublin, Ireland) who began by outlining ECT in general: "The big issue with ECT is that it is used for patients who have failed everything else. Patients on their third, fourth or fifth antidepressant or augmentation strategy can improve their chances of remission from 10-20% to 50% with ECT."[4]

He then described the difference between the two most commonly used configurations of ECT electrode placements: "The most widely used ECT is the moderate dose bi-temporal ECT, but more recent refinements in dose and electrode placement, such as right unilateral (RUL) placement and high dose stimuli ECT have been developed in order to reduce cognitive effects and make the treatment more tolerable."

ECT doses are determined for the patient using their individual seizure threshold, and bilateral electrode placement usually has a 1.5-times seizure threshold. However, RUL needs to be more liberal, at around six-times the seizure threshold, or else efficacy is not reached.

Professor McLoughlin then talked about the EFFECT-Dep study, in which the clinical effectiveness and side effects of these two techniques were compared: "The trial is the largest ECT trial to take place in Europe," he said. "And what we wanted to do in particular was a real world-trial with a pragmatic design, as opposed to patients being taken off all their medication, or patients only participating if they'd had a certain number of treatments. The other real-world feature was that it was a non-inferiority randomised control trial.

"We chose this method so we could see if the high-dose unilateral method is as good as the bilateral method, and with fewer side effects. If so, then it might make it more preferable, especially from a patient point of view. And what we found was that it was not inferior to standard conventional treatment, indeed and it had cognitive advantages, particularly with regard to retrograde amnesia."

Professor McLoughlin added: "Depressed patients have existing cognitive deficits, and furthermore, the side-effects with ECT resolved within a few weeks after finishing treatment."[5] In addition, an ongoing meta-analysis of high-dose, brief pulse, unilateral ECT trials to date demonstrates that this technique is as effective as bilateral ECT with clear advantage with regard to cognitive function or side effects.

Encouragingly, Professor McLoughlin's trial had a 99% retention rate during both trial and treatment period, which only dropped to 75% in the 12-month follow-up period. Recommending a shift in practice, Professor McLoughlin believes that from a clinical point of view, high-dose, unilateral ECT should be the first line of ECT to be used in depression, "It might make the treatment more acceptable to patients and their families."

Since its inception in 1938, one of the most important

Continued on page 14

CLINICAL TREATMENT

S.05: **Electroconvulsive therapy – achieving and maintaining the benefit** Auditorium **Sunday 09:00–10:40**

ECT reconsidered: Modern techniques for severe depression

Continued from page 13

advances in ECT technique has been the modification of the electrical stimulus, from a long pulse width (8ms) sine-wave stimulus to a 'brief' pulse width (0.5–1.5ms), or ultra-brief (0.3ms) square-wave stimulus. With this development, efficacy was preserved while cognitive side effects were markedly reduced.

Pascal Sienaert (Universitair Psychiatrisch Centrum, Kortenberg, Belgium) spoke to ECNP Daily news about studies investigating the efficacy of ultra-brief pulse (UPB) stimulus versus brief pulse (BP) stimulus. What he found when using a broad cognitive battery was that the UBP stimulus caused no significant change in cognitive function. "Normally we see a cognitive decline after the finishing the course of standard ECT,(5) so It was reassuring that with the UBP we could have an effective treatment, and reduce the in cognitive side effects," he said.

> "We saw that the brief pulse did better than ultra brief pulse group due to stronger efficacy."
>
> Pascal Sienaert

Professor Sienaert's core work was done in collaboration with Dr Stek and Dr Spaans (Parnassia Psychiatric Institute, The Hague, the Netherlands) who lead a study comparing UBP with BP. "We saw that the BP group did better than the UBP group due to stronger efficacy," commented Professor Sienaert.

A recent meta-analysis confirms that "classic" BP techniques are faster and more efficacious than UBP.[6] Recommending a cautious approach to selecting ECT methods, Professor Sienaert noted: "For suicidality and severe depression we need rapid techniques. We prefer standard pulse techniques because remission is higher, and fewer treatments are needed, however the side-effects are worse. Looking at current practice we see that many people have changed, and already adopted UBP as standard practice. But I think it's too early because you might win on side effects – most of which are temporary – but lose on efficacy and speed."

Professor Sienaert concluded by giving his future perspectives on individualised treatment with ECT: "What is reported in studies is the mean change, and on the whole we see three groups: some improve, some don't change, and some get worse. In the future we need to find predictive biomarkers for stratifying patients based on predicted responses to ECT. We can already broadly see which patient groups respond to best to particular treatments (for example, psychomotor retardation and psychosis) but we need to study signs that will let us know who will do well from ECT on an individual basis."

ECT is extremely effective in severely depressed elderly patients, however the cognitive side effects, particularly amnesia, are a concern in this demographic. Charles Kellner (Icahn School of Medicine at Mount Sinai New York, USA) described his study that has been testing the efficacy of UBP RUL ECT in depressed elderly patients. "These are very seriously ill, treatment-resistant patients whose lives are seriously impacted by the condition," he said.

> "ECT very rapidly improved [patients'] suicidal ideation and attempts."
>
> Charles Kellner

In the study, depression severity was assessed using the Hamilton Depression Rating Scale (HAM-D), and neurocognitive functioning was tested by a comprehensive battery. These thorough clinical assessments provided excellent antidepressant efficacy data. Remission was determined using a priori remission criteria of a HAM-D score of 10 or less (on two or more occasions).

Professor Kellner studied the effectiveness of this treatment on elderly (average age 70) patients with unipolar depression (average HAM-D 31). RUL UBP ECT was performed with concurrent venlafaxine antidepressant, three times per week until remission was achieved.

The results were overwhelmingly positive: "Of these very ill patients, 12% of whom had psychotic depression, 62% remitted, and 70% were responders [50% drop in HAM-D score]. Patients got better really quickly and 20% remitted in four or fewer sessions. And among the remitters, the average number of ECT sessions was just 7.3."

Speaking specifically on the suicidal aspects of depression, Professor Kellner said: "They have suicidal ideation, at the beginning of the course only 23% scored zero for this item

FUTURE MEETINGS

CONGRESSES

29th ECNP Congress	17-20 September 2016, Vienna, Austria
30th ECNP Congress	2-5 September 2017, Paris, France
31st ECNP Congress	6-9 October 2018, Barcelona, Spain
32nd ECNP Congress	7-10 September 2019, Copenhagen, Denmark

WORKSHOPS

ECNP Workshop on Clinical Research Methods
4-6 November 2015, Barcelona, Spain

ECNP Workshop for Junior Scientists in Europe
17-20 March 2016, Nice, France
9-12 March 2017, Nice, France

SCHOOLS

ECNP School of Child and Adolescent Neuropsychopharmacology
3-8 April 2016, Venice, Italy
2-7 April 2017, Venice, Italy

ECNP School of Old Age Neuropsychopharmacology
7-12 May 2017, Venice, Italy

ECNP School of Neuropsychopharmacology
26 June-1 July 2016, Oxford, United Kingdom
25-30 June 2017, Oxford, United Kingdom

SEMINARS
9-11 October 2015, Ukraine
30 October-1 November 2015, Portugal
6-8 November 2015, Moldova

OTHER MEETING

Neuroscience and Psychotherapy
20-21 March 2016, Nice, France

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in the HAM-D rating, which this rose to 84% after their course of ECT. It very rapidly improved their suicidal ideation and attempts."

Commenting on the lack mainstream use of ECT he added that it has been stigmatised for many decades, and suffered a tremendous amount of misinformation and prejudice. As such, he believes that ECT should be brought into the forefront of mainstream psychiatry, backed with adequate research funding and educational promotion from the ground level, both by physicians in psychiatric residencies, and students in medical school.

Professor Kellner went on to note that relapse rates after successful ECT are high,[7] and without active treatment, virtually all remitted patients relapse.

Also speaking during the session was Malek Bajbouj (Charité - Universitaetsmedizin Berlin, Germany), who described his research assessing the efficacy of different maintenance treatments after successful remittance with ECT.

"We carried out a trial in in-patients that had been successfully treated with ECT, going with the hypothesis that simultaneous techniques may provide more sustainable maintenance after ECT," he said, going on to explain that they chose RUL UPB ECT to minimise side effects, even though many more treatments were required to reach the efficacy of standard ECT.

"The idea was to test whether a combined approach would work best. The patients who were successfully treated with ECT were assigned to one of three arms: an antidepressant medication only group, an antidepressant medication combined with cognitive behavioural therapy (CBT) group, or an antidepressant medication combined with maintenance ECT group. The primary outcome was sustained remission at 12 months."

The results showed that CBT maintained a far stronger antidepressant effect than that of antidepressant medication or maintenance ECT combined with antidepressant medication, although they need to be confirmed with a larger trial, including patients who have more individualised ECT therapies. Professor Bajbouj commented: "These surprising results are very positive with regards to sustainable maintenance treatment after ECT."

Professor Bajbouj, speaking of the severity of his patients' depression, said: "Psychotherapy would never have been a course of action for these individuals without successful ECT treatment. CBT was used at a particular time-point after severity was lessened, and the mechanisms are completely different. CBT works on networks via prefrontal cortices whereas the mode of action of ECT is unclear."

> "These surprising results are very positive with regards to sustainable maintenance treatment after ECT."
>
> Malek Bajbouj

He concluded that the success of ECT is underpinned by robust maintenance of antidepressant effects, and the finding that CBT may be most efficacious method with regard to sustained remittance is very promising, both for the sustainability of the treatment and its acceptability in the long-run.

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PRECLINICAL RESEARCH

S.24: **The hub signalling protein mTOR in psychiatric disorders: friend or foe?** Emerald **Tuesday** 09:00–10:40

mTOR signalling shines a light on plasticity

A molecular approach to understanding how mammalian target of rapamycin (mTOR) regulates trophic changes in the dopaminergic system will take centre stage this morning at the 28th ECNP Congress. Concentrating on the association between addiction and neuroplasticity during the session will be Ginetta Collo (University of Brescia, Italy). During her presentation, Dr Collo will discuss the evidence for this association, while illustrating plastic changes and altered signalling mechanisms relevant in depression and addictive behaviour. "My talk is about mTOR, focusing on ketamine. Our very recent studies have now been analysed, and are being prepared for publication," she told *ECNP Daily News*.

Addictive drugs such as psychostimulants are known to alter the dopaminergic system both structurally and functionally, and these changes may underpin behavioural disturbances in addiction. Using amphetamine, cocaine and nicotine, Dr Collo and co-workers have already demonstrated activation of signalling pathways and changes in structural plasticity using in vitro cultured mesencephalic dopaminergic neurons.[1,2] NMDA receptor antagonist ketamine, although originally developed as an anaesthetic, also has psychotropic and addictive properties and has been shown to rapidly abate depressive symptoms in treatment-resistant depression.[3]

> "Ketamine is a drug of abuse, but is also used as antidepressant, forming a tight link to its plasticity-mediating properties."
> Ginetta Collo

Dr Collo continued: "Many antidepressants are known also to be effective in the dopamine system; studies in animal models showed that ketamine administration increased activation and plasticity in the frontal cortex.[4] We have been working on dopamine neurons and have data to show that direct and indirect agonists of dopamine increase dopamine release producing plasticity in dopamine neurons. So we were interested to see if ketamine, a drug known to have an effect on dopamine release also had such an effect on dopamine neurons."

Studies showing that exposure to stress causes neuronal atrophy in the hippocampus and the prefrontal cortex.[5] implicate a mechanistic role for dendrites and spines in depression, potentially contributing to the reduction in hippocampal and cortical volume. As such, ketamine may be a useful tool for revealing such mechanisms, as Dr Collo explained: "Ketamine is a drug of abuse, but is also used as antidepressant, forming a tight link to its plasticity-mediating properties, related both to addiction and stress-related plasticity changes."

As she described, Dr Collo was interested in studying whether ketamine's antidepressant effect could be partially mediated through increased plasticity. Two in vitro models were used to study ketamine's effect on plasticity: primary cultures of mesencephalic dopaminergic neurons prepared from 12.5 day mouse embryos; and dopaminergic neurons differentiated from cultured human pluripotent stem cells.

> "We found that ketamine increased the plasticity of dopamine neurons."
> Ginetta Collo

mTOR is a protein kinase involved in regulating many aspects of cell function such as growth, proliferation, motility, autophagy and transcription, and dysfunctional mTOR signalling may be involved in in neurological disease and disorders. Dr Collo went on to describe Western blot and immunofluorescence analysis of the phosphorylation of p70S6 kinase– the preferred substrate of mTORC1 which is involved in ribosomal biogenesis and protein translation. "We found that ketamine increased the plasticity of dopamine neurons; structurally we saw an increase in dendrite length and number, and soma size," she said.

"We also proved that ketamine increased the phosphorylation of p70S6 kinase, and this was blocked by pre-treatment with LY294002, a PI3-kinase inhibitor. Doing the same experiment in mouse and human cultures we have obtained the same results."

Dr Collo added, "Selective mTORC1 inhibitor rapamycin blocked the effect of ketamine on this plasticity and this effect is also mediated by BDNF." These data suggest a critical role of the mTOR pathway in mediating the structural remodelling of the dopamine system, a key neural substrate of addiction and psychosis

The dopamine D3 receptor is located in the limbic area and appears to mediate selective effects of drug-taking and drug-seeking behaviours, so that there has been considerable interest on the possible use of D3 receptor ligands to treat drug addiction. Expanding on her results, Dr Collo continued: "We also carried out a number of experiments where we showed involvement of these effects with the dopamine D3 receptor. The D3 receptor is expressed in dopamine neurons and involved in plastic effects of dopamine agonists, this been confirmed with in vivo and mouse and human cultures. In both models we can say that ketamine has an effect on structural plasticity and importantly – this effect is mediated by mTOR."

Emphasising this data she commented: "We think this is important because it gives another view not only for the cortex and striatum but also for the mesoencephalic and mesolimbic system addiction."

The relevance of such long-term structural changes is related to potential differences in reward and stress circuits for controlling motivation, which may eventually constitute a liability for drug taking relapse. Speaking of some prenatal exposure studies to cocaine and nicotine, Dr Collo said in closing: "We see still plasticity effects one to two weeks after mice are born. Some data shows prenatal exposure may predispose to more long-term plasticity changes, and this is very interesting. These may last into the next generation, this opens new prospects onto addiction."

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CLINICAL RESEARCH

E.02: **Advances in ADHD research across the lifespan** Elicium 1 **Sunday** 9:00–10:40

New perspectives on ADHD

The dissociation of symptoms and cognitive deficits

On Sunday, David Coghill (University of Dundee, UK) gave a comprehensive perspective of ADHD in adults, covering causality, treatment and diagnosis. Beginning with the long-term outlook, Dr Coghill pointed out that while ADHD prevalence declines in adulthood, many critical functional impairments remain and need to be recognised: "The persistence of ADHD is dependant on the definition of ADHD," he said. "If we look at the proportion of children who continue to meet the full diagnostic criteria at 25 years, it is quite low, about 15%.

"We're talking about the lifespan. We know the proportion of children with ADHD who continue to have significant ADHD-related functional impairments in adulthood is about 65%. This number is important for answering the parents and the child who ask, 'How long will it last?'"

Dr Coghill added: "Hyperactivity in children turns to an inner restlessness in adults."

With regards to clinical treatment, the Dr Coghill

CLINICAL RESEARCH

E.02: Advances in ADHD research across the lifespan Elicium 1 Sunday 9:00–10:40

showed that for 5-12 year olds, there was a sharp increase in the use of pharmacological treatment for ADHD between 2003-2008, though this has since plateaued. Despite this apparent increase, and with ADHD affecting 5% in the population, the concern is under-treatment with only 1% of children receiving pharmacological medication.

"The proportion of numbers being treated in the over 25 age group is very small, so the treatment of ADHD is dropping off as children grow up, but at a greater rate than one would expect them to," said Dr Coghill.

Moving on to consider the causes and neurobiology of ADHD, Dr Coghill illustrated the traditional linear causal pathways: alteration in genes and environment leading to changes in brain structure and function, which in turn affects cognition, and then presents symptoms. "We worked on a systematic review of ADHD, using the Bradford Hill criteria, but the evidence is not yet strong enough for us to pin down and ultimate causal factor," he commented.

"In fact, the only clear temporal association was prematurity in birth. Maternal smoking, low birth weight and some evidence for specific associations with different DNA variants only increase risk factors by 2-2.5 times. Even with ADHD's high heritability (75%), of the six genes we identified for causality, the increase in risk is very small – 3% overall causality, and 4% heritable causality."

Dr Coghill then pointed out the need to use extreme caution in examining and interpreting genetic associations: "Thapar and Rutter pointed out that there are other possible explanations for these associations that can not be excluded from these traditional designs.[1] We need to utilise designs that can separate pre- and post-natal effects because of high heritability; we need to use genetically sensitive designs to take into account the relationship between maternal and offspring genomes.

"Hyperactivity in children turns to an inner restlessness in adults."
David Coghill

"ADHD symptoms and cognitive deficits may be related but they don't sit in series as per the traditional hypothesis – rather they sit in parallel with each other, and this has important clinical implications."
David Coghill

"Obel et al. in 2011 carried out a very cleverly designed study to try and tease out the genetically sensitive impact smoking during pregnancy has on hyperkinetic disorder in Finland.[2] They found a significant association with those that had a genetic risk of ADHD and had smoked. However, they then used sibling-matched analyses to control for social and genetic confounding. They identified sibling pairs that were discordant for smoking to allow for the dissociation of genetic and environmental effects. When they did this, the association between smoking and ADHD disappeared. Mothers of children with ADHD have a higher likelihood of smoking which caused the apparent association."

Discussing the genetic influence, Dr Coghill commented: "Forty percent of ADHD heritability seems likely to be explained by common variants. Our understanding of the genetic liability of ADHD has changed over time – we now realise that while some come from rare chromosomal abnormalities, a significant portion comes from rare low frequency copy variants and about 40% from common variants. Preliminary analysis suggests one genome-wide significant locus."

ADHD is associated with clear developmental deficits, with poorer connectivity in many areas (ergo functional deficits). To that end, Dr Coghill described findings on the effect of methylphenidate on development: "While we have not shown that methylphenidate positively impacts brain development, it importantly doesn't negatively impact development," he said. "Using neuroimaging, Katja Rubia looked at ADHD medication and functionality and saw that functional changes elicited by stimulant medication were moving towards normalisation.[3]"

Questioning Barkley's Single model of inhibition, Dr Coghill talked about cognition: "Working in our own lab, looking at a broad range of cognitive deficits (working memory, inhibition, delay aversion, decision making, timing & variability), we found that none were either necessary or sufficient for ADHD, and if present they were independent of each other."

Moving onto treatment efficacy, Dr Coghill then noted that the correlation between cognitive and clinical change was very low: "In our study, over four years we showed that there were improvements in cognition and symptoms over time (and more so than healthy controls sometimes).[4] However, aside from changes in non executive recognition memory and symptoms, there was very little association between change in cognition and change in symptoms, This lead me to the hypothesis that ADHD symptoms and cognitive deficits may be related but they don't sit in series as per the traditional hypothesis – rather they sit in parallel with each other, and this has important clinical implications."

The dissociation between symptoms and cognition suggests that there may be more to ADHD than implied by the DSM or ICD criteria. From a treatment perspective, treatments that reduce ADHD symptoms may not improve cognition so there may be residual ADHD-related impairments and conversely, treatments that improve cognitive aspects may not also improve core ADHD symptoms.

Dr Coghill concluded by recommending medication as a first line of treatment in ADHD and allowing the option of cognitive treatment for less severe ADHD, which has shown to improve quality of life.

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AGENDA FOR 2016-2017

- **3-8 April 2016 and 2-7 April 2017**
  ECNP School of Child and Adolescent Neuropsychopharmacology,
  Venice, Italy
- **26 June-1 July 2016 and 25-30 June 2017**
  ECNP School of Neuropsychopharmacology
  Oxford, United Kingdom
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  ECNP School of Old Age Neuropsychopharmacology
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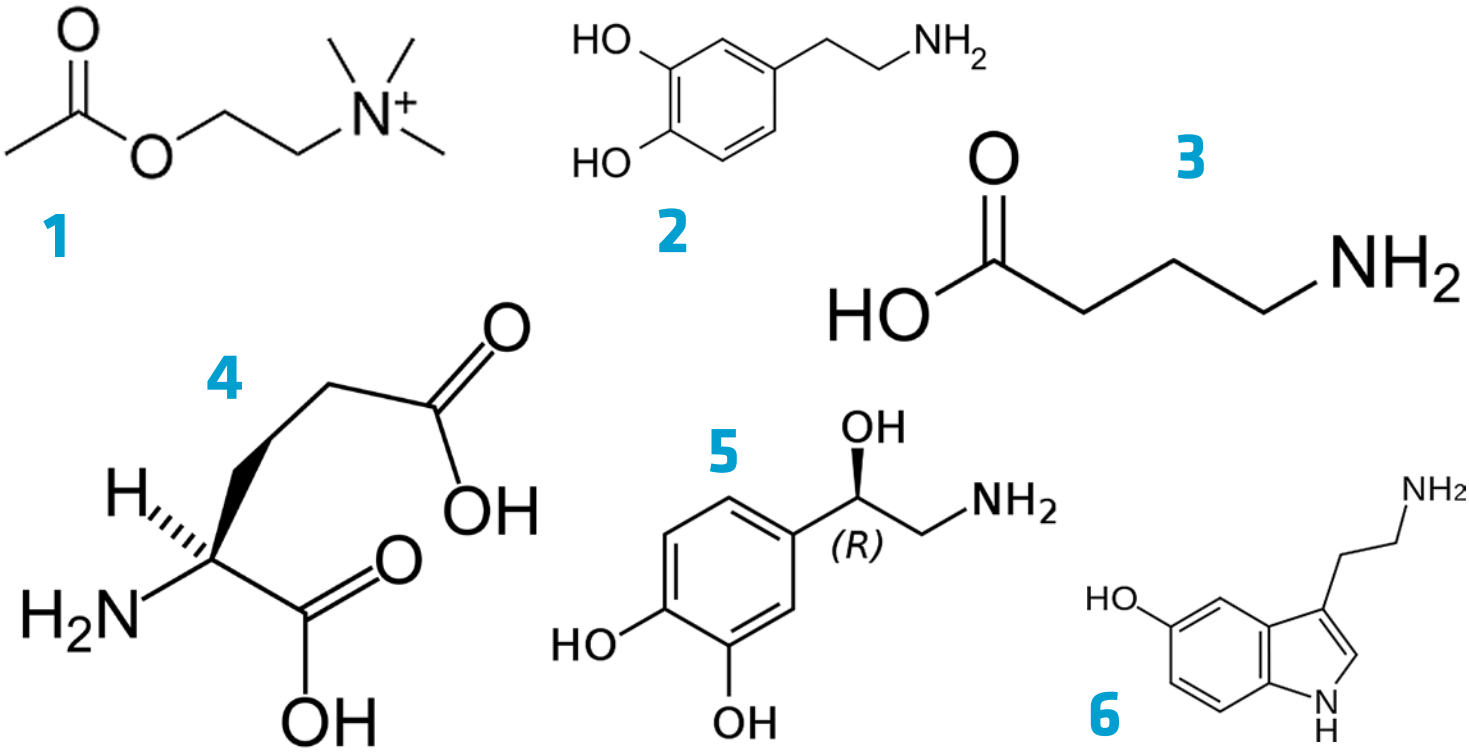
Can you identify these neurotransmitters by their chemical structure?



ECNP Daily News

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Answers to today's puzzle

1 Acetylcholine
2 Dopamine
3 GABA
4 Glutamate
5 Norepinephrine
6 Serotonin

Answers to puzzle from Issue 3

1 Hippocrates
2 Avicenna
3 Louis XIV of France
4 Benjamin Rush
5 Vladimir Bekhterev
6 Ivan Pavlov

TODAY'S PROGRAMME TUESDAY

TIME	ROOM	SESSION
07.45 - 08.45		**Brainstorming sessions**
	D201	BS.7 Individual variability in mice response to drugs: a hurdle or an advantage?
	D202	BS.8 Biomarkers: potential to enhance outcomes in treating depression
	D203	BS.9 Neurobiological characteristics of disruptive behaviour disorders: value for clinical practice
09.00 - 17.00	Exhibition area	**Exhibition**
09.00 - 10.40		**Symposia**
	Auditorium	CT S.21 Drug repurposing in CNS: how to maximise the benefits of serendipity and promiscuity
	Elicium 2	CR S.22 Neuroimaging characteristics of child and adolescent offspring of schizophrenia and bipolar disorder patients
	Forum	TR S.23 Stress as a risk factor: how much is enough?
	Emerald	PR S.24 The hub signalling protein mTOR in psychiatric disorders: friend or foe?
	Elicium 1	ET E.06 Psychopharmacology in pregnancy and post partum
10.40 - 11.15	Poster podium	**Travel award ceremony**
	Poster & exhibition areas	**Coffee break**
	Poster area	**Poster viewing**
11.15 - 12.00	Auditorium	**PL.05 Brain Prize plenary lecture** – Impulsivity and compulsivity: neural substrates and neuropsychiatric implications
12.00 - 14.00	Poster & exhibition areas	**Lunch**
12.15 - 13.45	Poster area	**Poster session**
12.15 - 12.45	Poster podium	**RF.03 Rapid-fire poster session**
12.15 - 13.00	Emerald	NS.01 How the Neuroscience-based Nomenclature can change my practice
13.00 - 13.15	Poster podium	**Poster award ceremony**
13.15 - 13.45	Poster podium	**CD.03 Career development session** – A job beyond research
14.00 - 14.45	Auditorium	**PL.06 Anna-Monika Award lecture I** – Anxious temperament: results from a translational neuroscience approach
14.45 - 15.00	Poster & exhibition areas	**Coffee break**
15.00 - 16.40		**Symposia**
	Auditorium	CT S.25 Pharmacological enhancement of fear extinction in anxiety disorders: where do we stand?
	Elicium 2	CR S.26 TNM symposium – Genetics, genomics, social stressors: opportunities for biomarkers of suicidal behaviour?
	Forum	TR S.27 Towards neuroimaging markers for diagnosis, prognosis and treatment prediction
	Emerald	PR S.28 Understanding the role of inflammation in the pathophysiology of depression
	Elicium 1	ET E.07 Atypical antipsychotic drugs – beyond the dopaminergic theory

CT CLINICAL TREATMENT TRACK CR CLINICAL RESEARCH TRACK TR TRANSLATIONAL RESEARCH TRACK PR PRECLINICAL RESEARCH TRACK ET EDUCATIONAL TRACK